ANDA 74-160

OCT 30 1997

Abbott Laboratories
Hospital Products Division
Attention: David T. Guzek
200 Abbott Park Road, D-389 AP30
Abbott Park, IL 60064-3537

Dear Sir:

This is in reference to your abbreviated new drug application dated December 30, 1991, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Bumetanide Injection USP, 0.25 mg/mL.

Reference is also made to your amendments dated March 28, 1996, April 1, 1997, May 13, 1997, and October 10, 1997.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Bumetanide Injection USP, 0.25 mg/mL, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Bumex® Injection, 0.25 mg/mL, of Hoffman LaRoche, Inc.).

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

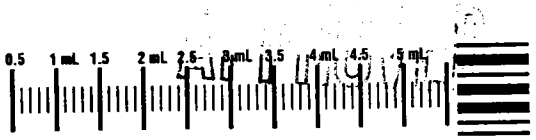
We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

Mango



4 mL Carpuject®

NDC 0074-1412-14

Abbott Laboratories, N. Chicago, IL 60064, USA RAO5649-2/R1-9/97

BUMETANIDE
Injection, USP

0074141214

FOR IV OR IM USE
PROTECT FROM LIGHT

1 mg/4 mL
0.25 mg per mL

OCT 30 1997

APPROVED

THIS END UP

B-477 NDC 0074-1412-14

10 Carpuject®

Sterile Cartridge-Needle Units

4 mL each

(Each with Sterile 22 Gauge 1¼ Inch Needle and Partially-Filled Cartridge of Medication)

DETECTO-SEAL® PAK Tamper Detection Package

Bumetanide Injection, USP

1 mg/4 mL

0.25 mg per mL

FOR IV OR IM USE

Caution: Federal law prohibits dispensing without prescription.

Bumetanide Injection, USP 1 mg/4 mL 0.25 mg per mL

(Each with Sterile 22 Gauge 1¼ Inch Needle and Partially-Filled Cartridge of Medication)

Bumetanide Injection, USP 1 mg/4 mL 0.25 mg per mL

(Each with Sterile 22 Gauge 1¼ Inch Needle and Partially-Filled Cartridge of Medication)

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Sterile Aqueo

Each mL contains C
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pH adjusted to appr

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Expiration date ar

RA05648-2/R1-9/97
Abbott Laboratories, Nor

OCT 30 1997

APPROVED

-14

Inch Needle
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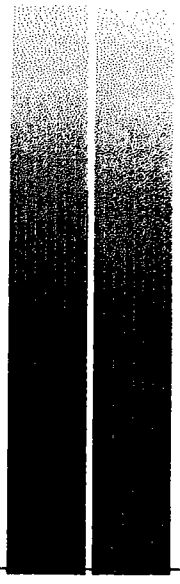

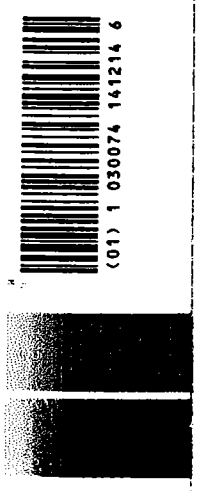

Bumetanide Injection, USP

1 mg /4 mL
0.25 mg per mL

(Each with Sterile **22 Gauge 1¼ Inch Needle** and Partially-Filled Cartridge of Medication)

Bumetanide Injection, USP

(Each with Sterile **22 Gauge 1¼ Inch Needle** and Partially-Filled Cartridge of Medication)

(Each with Sterile **22 Gauge 1¼ Inch Needle** and Partially-Filled Cartridge of Medication)

Bumetanide Injection, USP

1 mg /4 mL
0.25 mg per mL

Sterile Aqueous Injection

Each mL contains 0.25 mg bumetanide compounded with 0.85% sodium chloride and 0.4% ammonium acetate as buffers; 0.01% edetate disodium; 1% benzyl alcohol as preservative, and pH adjusted to approximately 7 with sodium hydroxide.

PROTECT FROM LIGHT. **Retain in carton until ready to use.**
Do not use if solution is discolored or contains a precipitate.
USUAL DOSAGE: For dosage recommendations and other important prescribing information, read accompanying insert.

Store at controlled room temperature 15°C to 30°C (59°F to 86°F).
Expiration date and lot number imprinted on bottom.

RA05648-2/R1-9/97
Abbott Laboratories, North Chicago, IL 60064, USA

EXPIRES
LOT

TO OPEN LIFT FLAP
TO CLOSE INSERT FLAP INTO CARTON

Bumetanide Injection, USP

1 mg /4 mL 0.25 mg per mL

(Each with Sterile **22 Gauge 1¼ Inch Needle** and Partially-Filled Cartridge of Medication)

OVERDOSAGE

Overdosage can lead to acute profound water loss, volume and electrolyte depletion, dehydration, reduction of blood volume and circulatory collapse with a possibility of vascular thrombosis and embolism. Electrolyte depletion may be manifested by weakness, dizziness, mental confusion, anorexia, lethargy, vomiting and cramps. Treatment consists of replacement of fluid and electrolyte losses by careful monitoring of the urine and electrolyte output and serum electrolyte levels.

DOSAGE AND ADMINISTRATION

Dosage should be individualized with careful monitoring of patient response.

Parenteral Administration: Bumetanide injection may be administered parenterally (IV or IM) to patients in whom gastrointestinal absorption may be impaired or in whom oral administration is not practical.

Parenteral treatment should be terminated and oral treatment instituted as soon as possible.

The usual initial dose is 0.5 mg to 1 mg intravenously or intramuscularly. Intravenous administration should be given over a period of 1 to 2 minutes. If the response to an initial dose is deemed insufficient, a second or third dose may be given at intervals of 2 to 3 hours, but should not exceed a daily dosage of 10 mg.

Miscibility and Parenteral Solutions: The compatibility tests of bumetanide injection with 5% Dextrose Injection, 0.9% Sodium Chloride Injection and Lactated Ringer's Injection in both glass and plasticized PVC (Viaflex) containers have shown no significant absorption effect with either containers, nor a measurable loss of potency due to degradation of the drug. However, solutions should be freshly prepared and used within 24 hours.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

HOW SUPPLIED

Bumetanide Injection, USP is available as:

1 mg/4 mL (0.25 mg/mL) (4 mL fill in 5 mL cartridge) CARPUJECT Sterile Cartridge-Needle Unit (22 Gauge 1 1/4 Inch Needle), box of 10 (L-1412)

Store at controlled room temperature 15°C to 30°C (59°F to 86°F). PROTECT FROM LIGHT. Retain in carton until ready to use.

Do not use the injection if it is discolored or contains a precipitate.

Caution: Federal (USA) law prohibits dispensing without prescription.

to USP 23
(Gen Chapter)

PDC #
0074-1412-1Y

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RAO5652-R1-Rev. Sept., 1997 Printed in USA

ABBOTT LABORATORIES, NORTH CHICAGO, IL 60064, USA

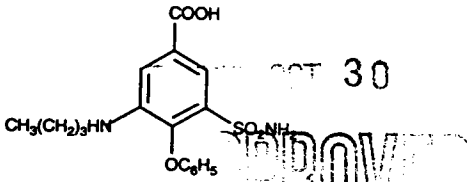
BUMETANIDE INJECTION, USP

WARNING: Bumetanide injection is a potent diuretic which, if given in excessive amounts, can lead to a profound diuresis with water and electrolyte depletion. Therefore, careful medical supervision is required, and dose and dosage schedule have to be adjusted to the individual patient's needs. (See **DOSAGE AND ADMINISTRATION.**)

DESCRIPTION

Bumetanide is a loop diuretic, available as 4 mL Carpuject® Sterile Cartridge-Needle unit, for intravenous or intramuscular injection as a sterile solution. Each mL contains 0.25 mg bumetanide compounded with 0.85% sodium chloride and 0.4% ammonium acetate as buffers; 0.01% edetate disodium; 1% benzyl alcohol as preservative, and pH adjusted to approximately 7 with sodium hydroxide.

Chemically, bumetanide is 3-(butylamino)-4-phenoxy-5-sulfamoylbenzoic acid. It is a practically white powder, slightly soluble in water; soluble in alkaline solutions, having a calculated molecular weight of 364.42 and a molecular formula of $C_{17}H_{20}N_2O_5S$. The structural formula is as follows:



OCT 30

PROV

CLINICAL PHARMACOLOGY

Bumetanide is a loop diuretic with a rapid onset and short duration of action. Pharmacological and clinical studies have shown that 1 mg bumetanide has a diuretic potency equivalent to approximately 40 mg furosemide. The major site of bumetanide action is the ascending limb of the loop of Henle.

The mode of action has been determined through various clearance studies in both humans and experimental animals. Bumetanide inhibits sodium reabsorption in the ascending limb of the loop of Henle, as shown by marked reduction of free-water clearance ($^{C}H_2O$) during hydration and tubular free-water reabsorption ($T^{C}H_2O$) during hydropenia. Reabsorption of chloride in the ascending limb is also blocked by bumetanide, and bumetanide is somewhat more chloruretic than natriuretic.

Potassium excretion is also increased by bumetanide, in a dose-related fashion.

Bumetanide may have an additional action in the proximal tubule. Since phosphate reabsorption takes place largely in the proximal tubule, phosphaturia during bumetanide-induced diuresis is indicative of this additional action. This is further supported by the reduction in the renal clearance of bumetanide by probenecid, associated with diminution in the natriuretic response. This proximal tubular activity does not seem to be related to an inhibition of carbonic anhydrase. Bumetanide does not appear to have a noticeable action on the distal tubule.

Bumetanide decreases uric acid excretion and increases serum uric acid. Diuresis starts within minutes following an intravenous injection and reaches maximum levels within 15 to 30 minutes.

Several pharmacokinetic studies have shown that bumetanide, administered orally or parenterally, is eliminated rapidly in humans, with a half-life of between 1 and 1 1/2 hours. Plasma protein-binding is in the range of 94% to 96%.

Oral administration of carbon-14 labeled bumetanide to human volunteers revealed that 81% of the administered radioactivity was excreted in the urine, 45% of it as unchanged drug. Urinary and biliary metabolites identified in this study were formed by oxidation of the N-butyl side chain. Biliary excretion of bumetanide amounted to only 2% of the administered dose.

INDICATIONS AND USAGE

Bumetanide injection is indicated for the treatment of edema associated with congestive heart failure, hepatic and renal disease, including the nephrotic syndrome.

Almost equal diuretic response occurs after oral and parenteral administration of bumetanide. Therefore, if impaired gastrointestinal absorption is suspected or oral administration is not practical, bumetanide should be given by the intramuscular or intravenous route.

Successful treatment with bumetanide following instances of allergic reactions to furosemide suggests a lack of cross-sensitivity.

CONTRAINDICATIONS

Bumetanide is contraindicated in anuria. Although bumetanide can be used to induce diuresis in renal insufficiency, any marked increase in blood urea nitrogen or creatinine, or the development of oliguria during therapy of patients with progressive renal disease, is an indication for discontinuation of treatment with bumetanide. Bumetanide is also contraindicated in patients in hepatic coma or in states of severe electrolyte depletion until the condition is improved or corrected. Bumetanide is contraindicated in patients hypersensitive to this drug.

WARNINGS

1. Volume and electrolyte depletion. The dose of bumetanide should be adjusted to the patient's need. Excessive doses or too frequent administration can lead to profound water loss, electrolyte depletion, dehydration, reduction in blood volume and circulatory collapse with the possibility of vascular thrombosis and embolism, particularly in elderly patients.

2. Hypokalemia. Hypokalemia can occur as a consequence of bumetanide administration. Prevention of hypokalemia requires particular attention in the following conditions: patients receiving digitalis and diuretics for congestive heart failure, hepatic cirrhosis and ascites, states of aldosterone excess with normal renal function, potassium-losing nephropathy, certain diarrheal states, or other states where hypokalemia is thought to represent particular added risks to the patient, *i.e.*, history of ventricular arrhythmias.

In patients with hepatic cirrhosis and ascites, sudden alterations of electrolyte balance may precipitate hepatic encephalopathy and coma. Treatment in such patients is best initiated in the hospital with small doses and careful monitoring of the patient's clinical status and electrolyte balance. Supplemental potassium and/or spironolactone may prevent hypokalemia and metabolic alkalosis in these patients.

3. Ototoxicity. In cats, dogs, and guinea pigs, bumetanide has been shown to produce ototoxicity. In these test animals bumetanide was 5 to 6 times more potent than furosemide and, since the diuretic potency of bumetanide is about 40 to 60 times furosemide, it is anticipated that blood levels necessary to produce ototoxicity will rarely be achieved. The potential exists, however, and must be considered a risk of intravenous therapy, especially at high doses, repeated frequently in the face of renal excretory function impairment. Potentiation of aminoglycoside ototoxicity has not been tested for bumetanide. Like other members of this class of diuretics, bumetanide probably shares this risk.

4. Allergy to sulfonamides. Patients allergic to sulfonamides may show hypersensitivity to bumetanide.

5. Thrombocytopenia. Since there have been rare spontaneous reports of thrombocytopenia from postmarketing experience, patients should be observed regularly for possible occurrence of thrombocytopenia.

PRECAUTIONS

General: Serum potassium should be measured periodically and potassium supplements or potassium-sparing diuretics added if necessary. Periodic determinations of other electrolytes are advised in patients treated with high doses or for prolonged periods, particularly in those on low salt diets.

Hyperuricemia may occur; it has been asymptomatic in cases reported to date. Reversible elevations of the BUN and creatinine may also occur, especially in association with dehydration and particularly in patients with renal insufficiency. Bumetanide may increase urinary calcium excretion with resultant hypocalcemia.

Diuretics have been shown to increase the urinary excretion of magnesium; this may result in hypomagnesemia.

Laboratory Tests: Studies in normal subjects receiving bumetanide revealed no adverse effects on glucose tolerance, plasma insulin, glucagon and growth hormone levels, but the possibility of an effect on glucose metabolism exists. Periodic determinations of blood sugar should be done, particularly in patients with diabetes or suspected latent diabetes.

Patients under treatment should be observed regularly for possible occurrence of blood dyscrasias, liver damage, or idiosyncratic reactions, which have been reported occasionally in foreign marketing experience. The relationship of these occurrences to bumetanide use is not certain.

Drug Interactions:

1. Drugs with ototoxic potential (see **WARNINGS**): Especially in the presence of impaired renal function, the use of parenterally administered bumetanide in patients to whom aminoglycoside antibiotics are also being given should be avoided, except in life-threatening conditions.

2. Drugs with nephrotoxic potential: There has been no experience on the concurrent use of bumetanide with drugs known to have a nephrotoxic potential. Therefore, the simultaneous administration of these drugs should be avoided.

3. Lithium: Lithium should generally not be given with diuretics (such as bumetanide) because they reduce its renal clearance and add a high risk of lithium toxicity.

4. Probenecid: Pretreatment with probenecid reduces both the natriuresis and hyperreninemia produced by bumetanide. This antagonistic effect of probenecid on bumetanide natriuresis is not due to a direct action on sodium excretion but is probably secondary to its inhibitory effect on renal tubular secretion of bumetanide. Thus, probenecid should not be administered concurrently with bumetanide.

5. Indomethacin: Indomethacin blunts the increases in urine volume and sodium excretion seen during bumetanide treatment and inhibits the bumetanide-induced increase in plasma renin activity. Concurrent therapy with bumetanide is thus not recommended.

6. Antihypertensives: Bumetanide may potentiate the effect of various antihypertensive drugs, necessitating a reduction in the dosage of these drugs.

7. Digoxin: Interaction studies in humans have shown no effect on digoxin blood levels.

8. Anticoagulants: Interaction studies in humans have shown bumetanide to have no effect on warfarin metabolism or on plasma prothrombin activity.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Bumetanide was devoid of mutagenic activity in various strains of *Salmonella typhimurium* when tested in the presence or absence of an *in vitro* metabolic activation system. An 18-month study showed an increase in mammary adenomas of questionable significance in female rats receiving oral doses of 60 mg/kg/day (2000 times a 2 mg human dose). A repeat study at the same doses failed to duplicate this finding.

Reproduction studies were performed to evaluate general reproductive performance and fertility in rats at oral dose levels of 10, 30, 60, or 100 mg/kg/day. The pregnancy rate was slightly decreased in the treated animals; however, the differences were small and not statistically significant.

Pregnancy: Teratogenic Effects: Pregnancy Category C. Bumetanide is neither teratogenic nor embryocidal in mice when given in doses up to 3400 times the maximum human therapeutic dose.

Bumetanide has been shown to be nonteratogenic, but it has a slight embryocidal effect in rats when given in doses of 3400 times the maximum human therapeutic dose and in rabbits at doses of 3.4 times the maximum human therapeutic dose. In one study, moderate growth retardation and increased incidence of delayed ossification of sternebrae were observed in rats at oral doses of 100 mg/kg/day, 3400 times the maximum human therapeutic dose. These effects were associated with maternal weight reductions noted during dosing. No such adverse effects were observed at 30 mg/kg/day (1000 times the maximum human therapeutic dose). No fetotoxicity was observed at 1000 to 2000 times the human therapeutic dose.

In rabbits, a dose-related decrease in litter size and an increase in resorption rate were noted at oral doses of 0.1 mg/kg/day and 0.3 mg/kg/day (3.4 and 10 times the maximum human therapeutic dose). A slightly increased incidence of delayed ossification of sternebrae occurred at 0.3 mg/kg/day; however, no such adverse effects were observed at the dose of 0.03 mg/kg/day. The sensitivity of the rabbit to bumetanide parallels the marked pharmacologic and toxicologic effects of the drug in this species.

Bumetanide was not teratogenic in the hamster at an oral dose of 0.5 mg/kg/day (17 times the maximum human therapeutic dose). Bumetanide was not teratogenic when given intravenously to mice and rats at doses up to 140 times the maximum human therapeutic dose.

There are no adequate and well-controlled studies in pregnant women. A small investigational experience in the United States and marketing experience in other countries to date have not indicated any evidence of adverse effects on the fetus, but these data do not rule out the possibility of harmful effects. Bumetanide should be given to a pregnant woman only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether this drug is excreted in human milk. As a general rule, nursing should not be undertaken while the patient is on bumetanide since it may be excreted in human milk.

Pediatric Use: Safety and effectiveness in children below the age of 18 have not been established.

ADVERSE REACTIONS

The most frequent clinical adverse reactions considered probably or possibly related to bumetanide are muscle cramps (seen in 1.1% of treated patients), dizziness (1.1%), hypotension (0.8%), headache (0.6%), nausea (0.6%), and encephalopathy (in patients with preexisting liver disease) (0.6%). One or more of these adverse reactions have been reported in approximately 4.1% of bumetanide-treated patients.

Less frequent clinical adverse reactions to bumetanide are impaired hearing (0.5%), pruritus (0.4%), electrocardiogram changes (0.4%), weakness (0.2%), hives (0.2%), abdominal pain (0.2%), arthritic pain (0.2%), musculoskeletal pain (0.2%), rash (0.2%) and vomiting (0.2%). One or more of these adverse reactions have been reported in approximately 2.9% of bumetanide-treated patients.

Other clinical adverse reactions, which have each occurred in approximately 0.1% of patients, are vertigo, chest pain, ear discomfort, fatigue, dehydration, sweating, hyperventilation, dry mouth, upset stomach, renal failure, asterixis, itching, nipple tenderness, diarrhea, premature ejaculation and difficulty maintaining an erection.

Laboratory abnormalities reported have included hyperuricemia (in 18.4% of patients tested), hypochloremia (14.9%), hypokalemia (14.7%), azotemia (10.6%), hyponatremia (9.2%), increased serum creatinine (7.4%), hyperglycemia (6.6%), and variations in phosphorus (4.5%), CO_2 content (4.3%), bicarbonate (3.1%) and calcium (2.4%). Although manifestations of the pharmacologic action of bumetanide, these conditions may become more pronounced by intensive therapy.

Also reported have been thrombocytopenia (0.2%) and deviations in hemoglobin (0.8%), prothrombin time (0.8%), hematocrit (0.6%), WBC (0.3%) and differential counts (0.1%). There have been rare spontaneous reports of thrombocytopenia from postmarketing experience.

Diuresis induced by bumetanide may also rarely be accompanied by changes in LDH (1%), total serum bilirubin (0.8%), serum proteins (0.7%), SGOT (0.6%), SGPT (0.5%), alkaline phosphatase (0.4%), cholesterol (0.4%) and creatinine clearance (0.3%). Increases in urinary glucose (0.7%) and urinary protein (0.3%) have also been seen.

U 14

ANDA APPROVAL SUMMARY

ANDA: 74-160 **DRUG PRODUCT:** Bumetanide Injection USP

FIRM: Abbott Laboratories **DOSAGE FORM:** injection
STRENGTH: 0.25 mg/mL

CGMP STATEMENT/EIR UPDATE STATUS: PENDING

BIO STUDY: Office Level Bio Review 03-25-96

VALIDATION: N/A

STABILITY: The specified market containers are used in stability.

Expiration: 24 months; based on 3 months accelerated data

Specifications:
- Assay:
- pH:
- Benzyl Alcohol:
- Edetate Disodium:
- Sterility
- Endotoxins
- Degradation Products:
- Chromatographic Purity:

LABELING: Satisfactory on 08-16-95

STERILIZATION VALIDATION: Micro Review APPROVAL 03-06-96

SIZE OF BIOBATCH: ADEQUATE

SIZE OF STABILITY BATCHES: The size and packaging of the stability bathes would not meet todays standards. However, these were adequate for the time at which the batch was manufactured.

PROPOSED PRODUCTION BATCH: The manufacturing process is the same as that used for the stability batch.

CHEMIST:
TEAM LEADER:

0 IV

1. CHEMISTRY REVIEW NO 5 2. ANDA 74-160

3. NAME AND ADDRESS OF APPLICANT
Abbott Laboratories
Attention: David T. Gerzek
D-389, Bldg, AP30
200 Abbott Park Road
Abbott Park, IL 60064

4. LEGAL BASIS FOR SUBMISSION Bumex® Injection;
Roche Laboratories

5. SUPPLEMENT(s) N/A 8. SUPPLEMENT(s) PROVIDE(s) FOR: N/A

6. PROPRIETARY NAME none

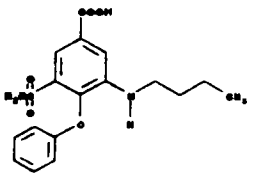
7. NONPROPRIETARY NAME **Bumetanide Injection USP**

10. PHARMACOLOGICAL CATEGORY: diuretic 11. Rx or OTC: Rx

12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM injection 14. POTENCY **0.25 mg/mL**

15. CHEMICAL NAME AND STRUCTURE
Bumetanide USP
$C_{17}H_{20}N_2O_5S$; M.W. = 364.42, CAS [28395-03-1]
3-(Butylamino)-4-phenoxy-5-sulfamoylbenzoic acid



16. RECORDS AND REPORTS N/A

17. COMMENTS The EER was not acceptable because of the DS supplier. Therefore, the firm withdrew the DS supplier and adds a new DS supplier in the 04-01-97 minor amendment.

18. CONCLUSIONS AND RECOMMENDATIONS **APPROVABLE, pending EER**

19. REVIEWER: Melissa Maust DATE COMPLETED: June 5, 1997

cc: ANDA 74-160
ANDA 74-160/DUP Jacket
Field Copy

Endorsements:
HFD-623/M.Maust/
HFD-623/V. Sayeed, PhD./

X:\NEW\FIRMSNZ\SANOFI\LTRS&REV\74160R5.APP
F/T by

D, V

APPROVAL SUMMARY

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 74-160 Date of Submission: October 10, 1997

Applicant's Name: Abbott Laboratories

Established Name: Bumetanide Injection USP, 0.25 mg/mL

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

A. Do you have 12 Final Printed Labels and Labeling? Yes

CONTAINER LABELS: 4 mL (1 mg/4 mL)

Satisfactory in FPL as of 10/10/97 submission

CARTON LABELING: 10 Carpuject®

Satisfactory in FPL as of 10/10/97 submission

PROFESSIONAL PACKAGE INSERT LABELING:

Satisfactory in FPL as of 10/10/97 submission

B. REVISIONS NEEDED POST-APPROVAL: - INSERT

1. DOSAGE AND ADMINISTRATION - Fifth paragraph:

... injection with Dextrose (5%) Injection, sodium Chloride (0.9%) Injection, ... [based on the General Chapter in USP 23]

2. HOW SUPPLIED

Complete the NDC number (*i.e.* 0074-1412-14).

C. BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Bumex® Injection

NDA Number: 18-226

NDA Drug Name: Bumex® Injection

NDA Firm: Roche Laboratories

Date of Approval of NDA Insert and supplement #: October 21, 1993/S-018

Has this been verified by the MIS system for the NDA?
Yes

Was this approval based upon an OGD labeling guidance?
No

Basis of Approval for the Container Labels: Bumex® Injection

Basis of Approval for the Carton Labeling: Bumex® Injection

Other Comments:

The ownership of this unapproved application has been transferred from Sanofi Pharmaceuticals, Inc. to Abbott Laboratories as of June 10, 1997. Refer to the letter from the firm dated June 18, 1997.

FOR THE RECORD:

a. This review was based on the labeling of Bumex® revised 4/93; approved 10/21/93, with minor modifications, and the firm's labels and labeling submitted on March 23, 1995, which was declared satisfactory for approval.

b. The ownership of this unapproved application has been transferred from Sanofi Pharmaceuticals, Inc. to Abbott Laboratories as of June 10, 1997. Refer to the letter from the firm dated June 18, 1997. The revised labels and labeling submitted on October 10, 1997 reflects this change of the ownership.

c. PATENTS/EXCLUSIVITIES

No pending issue. The firm's statement is accurate.

d. This is the only ANDA (or NDA) for a cartridge dosage form for this drug.

e. This drug product is light-sensitive.

f. Storage/dispensing recommendations:

NDA: Store at 59° to 86°F

ANDA: Store at controlled room temperature 15° to 30°C (59° to 86°F). PROTECT FROM LIGHT. Retain in carton until ready to use.

USP: Protect from light (Type 1 glass preferred)

g. PACKAGING CONFIGURATIONS

NDA - Ampules (2 mL, Boxes of 10), Vials (2 mL, boxes of 10; 4 mL, boxes of 10; 10 mL, boxes of 10)

ANDA - 4 mL Syringes (boxes of 10)

Date of Review: October 17, 1997 **Date of Submission: October 10, 1997**

Cycle # 4 (FPL)

Primary Reviewer: Chan Park **Date:**

Team Leader: John Grace **Date:**

---

cc:

ANDA: 74-160
DUP/DIVISION FILE
HFD-613/CPark/JGrace (no cc)
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Review

Bumetanide Injection, USP
0.25 mg/ml, 4 ml fill in
5 ml Carpuject Cartridge
ANDA # 74-160
Reviewer: James E. Chaney
WP # 74160W.692

Sterling Winthrop Inc.
New York, NY
Submission Date:
December 30, 1991

Review of a Waiver Request for an Injectable Dosage Form

The firm has requested that the in-vivo bioequivalence requirements for the product be waived under the provisions of 21 CFR 320.22(b)(1). The reference product is Bumex® 0.25 mg/ml, manufactured by Roche Laboratories.

Bumetanide is indicated for the treatment of edema associated with congestive heart failure, hepatic and renal disease, including the nephrotic syndrome.

Both products are solutions labelled for intramuscular and intravenous administration.

The formulations of test product and the reference product are as follows:

Ingredients:	Test Product	Reference Product
Bumetanide	0.25 mg/ml	0.25 mg/ml
Sodium Chloride	8.5 %	8.5 %
Ammonium Acetate	0.4 %	0.4 %
Disodium Edetate	0.01 %	0.01 %
Benzyl Alcohol	1 %	1 %
Sodium Hydroxide	pH adjustment to approx 7	
Water	q.s.	q.s.

Recommendation:

The Division of Bioequivalence agrees that the information submitted by Sterling Winthrop, Inc. demonstrates that Bumetanide Injection, USP, 0.25 mg/ml, 4 ml fill in 5 ml Carpuject cartridge falls under 21 CFR Section 320.22(b)(1) of the Bioavailability/ Bioequivalence Regulations. The waiver of the in-vivo bioequivalence study for the 0.25 mg/ml injection of the test product is granted. From the bioequivalence point of view, the Division of Bioequivalence deems the test injectable formulation to be bioequivalent to Bumex®, 0.25 mg/ml, manufactured by Roche Laboratories.

The firm should be advised of the recommendation.

James E. Chaney, Ph.D.
Division of Bioequivalence
Review Branch I

RD INITIALED A. Wu
FT INITIALED A. Wu

Date: 10/28/92

cc: ANDA 74-160 original, HFD-630, HFD-600 (OGD, Hare), HFD-22 (Hooten), HFD-652 (Wu, Chaney), HFC-130 (Allen), Drug File

JEC/102892/ntp/102892/WP #74160W.692